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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,389	10/07/2003	John H. Kenten	IGN-2005US02	7446

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,389	KENTEN ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80 and 94-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80 and 94-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/08/2006 has been entered.

2. Claims 1-79 and 81-93 have been cancelled. Claims 80 and 94 have been amended.

Claims 80 and 94-101 are pending and under examination.

Claim Rejections - 35 USC § 112, 2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

4. Claims 80 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons of record set forth in the final action.

Applicants argue that the amendment to recite "one epitope-containing segment" overcomes the rejection.

Applicants' argument is acknowledged, however the above amendment does not render the claimed definite because the recitation of "one epitope-containing segment" is the same as the recitation of "single epitope-containing segment". The claim can still be interpreted as being drawn to (i) a segment comprising one epitope, in which case the terms "a single epitope-containing segment comprising two or more identical or non-identical epitopes" does not make sense, or (ii) a segment comprising two or more epitopes. Amending the claim to recite "an epitope-containing segment" would obviate this rejection.

Claims 101 and 95-100 are rejected for being directly or indirectly dependent from claims 80 or 94, respectively.

Claim Rejections - 35 USC § 112, new matter

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 94 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the

application". Specifically, the amendment to the claim to include the term "non-imortalized" is considered new matter.

It is noted that, although the method steps are the same, the scope embraced by claim 94 is changed from a method of reducing the levels of a predetermined protein to a method of neutralizing the biological function of a predetermined protein. Applicants point to paragraphs 0022, 0024, 0036 and to Example 1 for support. It is noted that the indicated passages do recite "neutralizing antibodies", however this is in the general context of selecting epitopes that are known to be target for neutralizing antibodies and not in the context of neutralizing the activity of a predetermined protein. Example 1 is drawn to antibodies raised against a neutralizing HIV gp120 epitope, wherein the antibodies are tested by ELISA. However, Example 1 does not demonstrate that these antibodies are capable of neutralizing the activity of HIV gp120 and therefore does not provide support for the recitation of neutralizing the activity of a predetermined protein. Just because an antibody is neutralizing does not necessarily mean that the antibody will neutralize the function of a protein (i.e., completely eliminate its function). A neutralizing antibody will reduce, but not necessarily eliminate the function of its cognate protein. A search of the remaining portions of the specification failed to provide the necessary support. It is noted that the specification provides support for a method of reducing the biological function of a predetermined protein. Specifically, Example 6 demonstrate that the immunization of piglets with ubiquitin-GnRH fusion protein leads to significant reduction in testicular weight and serum testosterone levels; however, these results do not necessarily demonstrate that the function of GnRH was eliminated.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

** It is noted that the Applicant amended the claims to recite: "neutralizing the biological activity of a predetermined protein" to conform to the scope of the enablement as set forth in the final Office action and to advance the prosecution. However, upon further consideration, the Examiner agrees with the Applicant that such an enablement rejection should not have been made.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 80 and 101 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnston et al. (U.S. Patent No. 5,703,057, of record) for the reasons of record set forth in the final Office action.

Applicant argues that Johnston et al. do not teach elements of the present invention. Applicant argues that they found that a mere use of a fusion protein comprising one or more epitopes and ubiquitin, as taught by Johnston et al., does not result in optimal performance when the fusion protein is administered to a subject. Applicants argue that they have found via empirical research that a fusion protein comprising a heat shock protein such as ubiquitin fused to epitopes in a defined manner is useful for the stimulation of a specific immune response and that the bulk of the specification is directed to teaching and exemplification of this defined manner in which the claimed fusion proteins are made and used, for example that the ubiquitin fusion protein needs to be tolerated both systemically (i.e., tolerated by the immune system) and functionally (i.e., behave in a manner analogous to the wild-type ubiquitin). Applicants submit that Johnston et al. do not teach any of these defined manners in which the fusion proteins of claims 80 and 101 are made and therefore, Johnston et al. cannot be considered anticipatory art for the present invention.

Applicants' arguments are acknowledged, however claims 80 and 101 do not recite the defined manner in which the fusion proteins are made and used. When the claims are examined in their broadest reasonable interpretation, they are clearly anticipated by Johnston et al. The claims, as written, are drawn to a fusion protein comprising a heat shock protein fused to two or more non-contiguous epitope-containing segments, wherein each segment comprises one or more non-identical epitopes and Johnston et al. disclose this (see the final Office action). Additionally, the claims do not require the stimulation of a specific immune response, nor do they recite that the fusion protein needs to be tolerated both systemically and functionally. For these reasons, the claimed invention is anticipated by Johnston et al.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 80, 94-97, and 99-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al., in view of each Ferro et al. (Eur J Cancer, 1997, 33: 1468-1478, of record), Tang et al. (Nature, 1992, 356: 152-154, of record), and Sacca (Cardiovascular Research, 1997, 36: 3-9, of record) for the reasons of record set forth in the final Office action.

Applicants argue that Johnston et al. do not teach important elements of the present invention, as claimed and that the cited secondary references do not teach or suggest these missing elements. Therefore, Applicants submit that the Examiner did not make a *prima facie* case of obviousness. Applicants argue that, even if the prior art would teach each element of the present invention (which it does not), a finding of obviousness requires that there must be a suggestion or motivation to combine the cited prior art references, that there must be a reasonable expectation of success, and that the reasons to combine and the expectation of success must come from the prior art. Applicants argue that Tang et al. do not provide a motivation to use a DNA and not a protein, and even if they did, Tang et al. do not provide any teaching or suggestion for the desirability of such a combination. Moreover, Applicant argues that the Examiner did not present any evidence that the prior art teaches the desirability of such a combination and that the Examiner presented no evidence that the art teaches a reasonable expectation of success. Applicants argue that Examiner cannot merely assume a reasonable expectation of success before conducting the actual research and testing that the combined teachings result in the fusion protein of the claimed invention.

Applicants' arguments are acknowledged, however their arguments are not persuasive for the reasons below.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Johnston et al. is applied as above. (it is noted that Johnston et al. teach DNA immunization). Johnston et al. teach that mammalian genes such as ubiquitin fused to epitope-containing segments facilitate expression in mammalian cells (column 5, lines 19-29). Although Johnston et al. do not teach that vaccines can be used to neutralize the biological activity of predetermined proteins, the prior art provides numerous examples in which both protein and DNA vaccines were used as contraceptive, for immunocastration,or for breast cancer treatment, wherein the vaccines are directed against specific hormones and neutralize their activity (i.e., the hormones are predetermined proteins). For example, Ferro et al. teach the immunoneutralization of GnRH for immunocastration and as a potential anti-tumor treatment (Abstract, p. 1475, column 1, p. 1477, column 2) and Tang et al. teach DNA vaccines against the human growth hormone (hGH). Moreover, Tang et al. clearly provide the motivation to replace a protein with a DNA in a vaccine because they teach that (i) the use of DNA vaccine is simple and shortens the time required to produce antibodies by eliminating the steps of protein purification and adjuvant administration and (ii) the genetic immunization is preferred because of a longer response and higher magnitude of antibody production or level of T-cell response (p. 154, column 1 bridging column 2; see also the prior Office action). Based on these teachings, one of skill in the art would have readily recognized the advantages of using a DNA vaccine versus a protein vaccine. Therefore, one of skill in the art would have been motivated to replace the protein (i.e., the GnRH) of

Ferro et al. with the DNA encoding for it to simplify the procedure and to obtained a prolonged immune response. Moreover, one of skill in the art would have been motivated to use the method of Johnston et al. because they teach the advantage of using ubiquitin fused to epitope-containing segments (see above). Therefore, the cited art teach the desirability and motivation to combine and by citing these references, the Examiner did provide evidence that one of skill in the art would have had the desirability and the motivation to combine the teachings of the prior art. The argument that one of skill in the art would not have been expected to have a reasonable expectation of success in combining the teachings of the art to obtain the instant composition and that the Examiner did not provide evidence that the teachings of the art provide a reasonable expectation of success is not found persuasive because it is just an argument and not evidence that this is indeed the case. The cited prior art does teach a reasonable expectation of success. Johnston et al. clearly teach their method of being successful in eliciting immune response with practically any DNA and Applicants provided no evidence as to why such a method cannot be used with a DNA encoded for GnRH. The following is a citation from MPEP:

2145 [R-3] Consideration of Applicant's Rebuttal Arguments

I. ARGUMENT DOES NOT REPLACE EVIDENCE WHERE EVIDENCE IS NECESSARY

Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of

obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence a appropriate affidavit or declaration.

With respect to the argument that the Examiner cannot assume a reasonable expectation of success in the absence of experimentation, it is noted that the Office does not have the facilities and resources to provide the factual evidence needed in order to determine and/or compare the specific activities of the instant invention versus the reference invention of Johnston et al. taken with Ferro et al., Tang et al., and Sacca. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed invention is different from the one taught by prior art and to establish the patentable differences. See *in re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ2d 1922(PTO Bd. Pat. App. & Int. 1989).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

12. Claims 80, 94, 98, 100, and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al., in view of both Hohlfeld (Multiple Sclerosis, 1996, 1: 376-378 of record) and Tang et al. for the reasons of record set forth in the final Office action.

Applicants argue that Johnston et al. do not teach important elements of the present invention, as claimed and that the cited secondary references do not teach or suggest these missing elements. Therefore, Applicants submit that the Examiner did not make a *prima facie* case of obviousness. Applicants argue that, even if the prior art

would teach each element of the present invention (which it does not), the Examiner failed to provide clear evidence that the cited references provide the necessary motivation to combine and the necessary reasonable expectation of success. Applicants continue arguing that the mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art teaches the desire to combine. Applicants submit that Hohfeld is not enough for finding a suggestion to combine because the reference does not provide the required motivation, nor does it teach or suggest the desire to combine and that that Examiner did not present any evidence that the prior art teaches the desirability of such a combination.

Applicants' arguments are acknowledged, however their arguments are not persuasive for the reasons below.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Johnston et al. is applied as above. (it is noted that Johnston et al. teach DNA immunization). Johnston et al. teach that mammalian genes such as ubiquitin fused to epitope-containing segments facilitate expression in mammalian cells. Although Johnston et al. do not teach that vaccines can be used to neutralize the biological activity of predetermined proteins, such as TNF-α, Hohlfeld teaches the use of antibodies to inhibit TNF-α activity (i.e., a method of neutralizing TNF-α biological

activity) as a treatment for multiple sclerosis. Although Hohlfeld teaches passive immunization (i.e., the use of antibodies), one of skill in the art would have been motivated to use a DNA vaccine to elicit neutralizing anti-TNF-α antibodies because the art teaches the advantage of using such vaccines to generate an immune response, for example that the use of DNA vaccine is simple and shortens the time required to produce antibodies by eliminating the steps of protein purification and adjuvant administration and that the genetic immunization is preferred because of a longer response and higher magnitude of antibody production or level of T-cell response (see Tang et al. and also above). Based on these teachings, one of skill in the art would have readily recognized the advantages of using a DNA vaccine versus passive immunization that requires a protein vaccine. Therefore, one of skill in the art would have been motivated to replace the antibodies of Hohlfeld with the DNA encoding for TNF-α to simplify the procedure and to obtain a prolonged immune response. Moreover, one of skill in the art would have been motivated to use the method of Johnston et al. because they teach the advantage of using ubiquitin fused to epitope-containing segments (see above). The argument that one of skill in the art would not have been expected to have a reasonable expectation of success in combining the teachings of the art to obtain the instant composition and that the Examiner did not provide evidence that the teachings of the art provide a reasonable expectation of success is not found persuasive because it is just an argument and not evidence that this is indeed the case. The cited prior art does teach a reasonable expectation of success. Johnston et al. clearly teach their method of being successful in eliciting

immune response with practically any DNA and Applicants provided no evidence as to why such a method cannot be used with a DNA encoded for TNF-α. As noted above, Applicants' arguments are not evidence. With respect to the argument that the Examiner cannot assume a reasonable expectation of success in the absence of experimentation, it is noted that the Office does not have the facilities and resources to provide the factual evidence needed in order to determine and/or compare the specific activities of the instant invention versus the reference invention of Johnston et al. taken with Hohlfeld and Tang et al. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed invention is different from the one taught by prior art and to establish the patentable differences. See *in re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ2d 1922(PTO Bd. Pat. App. & Int. 1989).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

13. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD